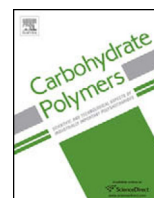




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Formation of spherical and core–shell polymeric microparticles from glycopolymers

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ABSTRACT

6-O-methacryloyl- α -D-glucoside **2** and 4-bromophenyl-6-O-methacryloyl-D-glucoside **7**, obtained by enzyme-catalyzed synthesis, have been homo-polymerized and copolymerized with styrene by a free radical process, yielding polymer materials with sugar moieties, attached to the polymer backbone via ester linkages. The results demonstrated that modifying the structural features of the monomers greatly affected the thermal and rheological properties of the polymers. The polymer materials obtained have been characterized by NMR, MALDI-MS, DSC, AFM, and EWC (equilibrium water content). The AFM images indicated the formation of spherical and core–shell polymeric microparticles.

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1. Introduction

Sugar-containing synthetic polymers have attracted great attention because of their potentials as biotechnological, pharmaceutical, and medical materials (Petrova, Correia-da-Silva, Crucho, & Barros, 2014; Varma, Kennedy, & Galgali, 2004; Wang, Dordick, & Linhardt, 2002). The developments in this field have been based on the advances in synthetic and polymer chemistry, and the past two decades have evidenced dramatic progress in the synthesis of functional glycopolymers (Stern & Jedrzejewski, 2008). The developments in polymerization techniques have enabled the synthesis of glycopolymers featuring a wide range of controlled architectures and functionalities (Ghadban & Albertin, 2013; Ladmiraal, Melia, & Haddleton, 2004; Narla, Nie, Li, & Sun, 2012). This class of sugar based polymers has been investigated for a variety of applications, particularly in the biomedical field (Ahmed, Wattanaarsakit, & Narain, 2013; Munoz-Bonilla, Ibarboure, Bordege, Fernandez-Garcia, & Rodriguez-Hernandez, 2010). The design of polymers and oligomers that mimic the complex structures and remarkable biological properties of natural polysaccharides is an important task with both fundamental and practical implications (Liao, Yu, & Guan, 2009; Oh, Sheng, Chang, & Hsieh-Wilson, 2013; Cameron et al., 2008). Therefore, many research groups are aiming to combine the advantages of natural compounds and synthetic systems to explore

the potential structural versatility available by synthetic chemistry (Ting, Chen, & Stenzel, 2010; Vazquez-Dorbatt, Lee, Lin, & Maynard, 2012; Zhang & Haddleton, 2013; Fogueri & Singh, 2009).

Self-assembly of amphiphilic polymers into colloidal nanoparticles constitutes a typical example of advanced functional polymers (Voit & Appelhans, 2010; Qing-He & Li-Yan, 2013). Each structural unit of the glycopolymer is an amphiphile consisting of hydrophilic carbohydrate and hydrophobic styryl moieties (Kobayashi, Sumitomo, & Ima, 1985). The field of nanostructure science and technology has been growing fast in the past few years (Brannon-Peppas & Blanchette, 2004; Chan, Valencia, Zhang, Langer, & Farokhzad, 2010; Panyama & Labhasetwar, 2012). As an example, glyco-nanoparticles, due to their versatile nature, could offer a platform for the design of carbohydrate-based vaccines (Sunasee & Narain, 2013).

To produce glycopolymers with sugars attached, polymerizable sugar derivative monomers need to be developed. Thus, several types of vinyl sugars have been investigated and a number of new compounds synthesized, as reviewed by Tokiwa and Kitagawa (2008). Wulff, Schmid, and Venhoff (1996) described vinyl sugars consisting of three units – bonding unit, spacer unit, and sugar unit. The sugar density in a polymer, its biodegradability and hydrophilicity are dependent on the type of vinyl sugar being used. Various kinds of polymers could be designed by modifying these three parts (Petrova, Correia-da-Silva, et al., 2014a). Amphiphilic glycopolymer poly(2-lactobionamidoethyl methacrylate-random-3-acrylamidophenyl boronic acid) (p(LAMA-r-AAPBA)), have been synthesized and investigated as vehicles for nasal delivery of

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peptides and proteins (Zhenga, Guoa, Wub, Suna, & Zhanga, 2013). Glycopolymers have been attached to iron oxide nanoparticle (IONP) surfaces and the specific binding of lectin to them have been studied (Basuki et al., 2014). Glycopolymer-stabilized gold nanoparticles as potential synthetic cancer vaccine have been designed as a peptide-free multivalent glycosylated nanoscale constructs (Parry, Clemson, Ellis, Bernhard, Davis, & Cameron, 2013).

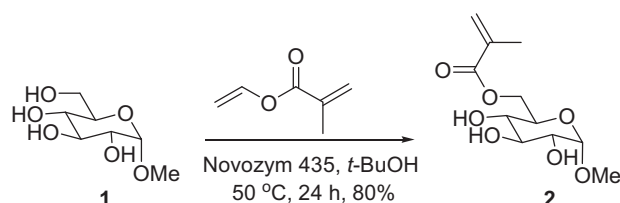
In the last decade, our group has focused on the synthesis of amphiphilic polymers with pending sugar moieties, as part of a program for valorization of carbohydrate derivatives as high value-added products (Barros & Petrova, 2009; Barros, Petrova, & Correia-da-Silva, 2011; Barros, Petrova, & Singh, 2010b; Peça, Petrova, Cardoso, & Barros, 2012; Petrova, Potewar, Ascenso, & Barros, 2014). Herein, various conditions for the free-radical polymerization and co-polymerization with styrene of two differently functionalized glucose monomers have been explored. The resulting polymer materials were characterized by NMR, MALDI-TOF, DSC, and EWC. Their ability to self-assemble into nanoparticles in water solutions has been studied using AFM (Munoz-Bonilla et al., 2010).

2. Results and discussion

2.1. Synthesis of monomers

The synthesis of methyl 6-*O*-methacryloyl- α -D-glucoside **2** (Scheme 1) was performed as described by Albertin, Stenzel, Barner-Kowollik, Foster, and Davis (2004). The lipase-catalyzed acylation of methyl α -D-glucoside **1** with vinyl methacrylate was performed in *tert*-butanol at 50 °C using Novozym 435 (a commercially available immobilized lipase), which can be easily recovered from the reaction medium by filtration. It is known for its ability to catalyze regioselective esterification and transesterification reactions and to provide excellent chemoselectivity toward the primary C-6 positions of glucose (Miura, Ikeda, & Kobayashi, 2003).

For the synthesis of 4-bromopheny-6-*O*-methacryloyl-D-glucoside **7** a sequence of known procedures was followed (Scheme 2). The substituent chosen is a mesogenic functional group, known to aid the self-organization of compounds, for example, in liquid crystals (van-Doren, Smits, Pestman, Engberts, & Kellog, 2000). The first step was per-*O*-acetylation of glucose in solvent-free conditions with a stoichiometric amount of acetic anhydride employing 1 mol% Cu(OTf)₂ at room temperature, as described by Tai, Kulkarni, and Hung (2003). The reaction proceeded smoothly with high yield (91%) to give exclusively the pyranosyl product as an anomeric mixture. The advantage of this procedure was that the use of pyridine as solvent and an excess of acetic anhydride was avoided, thus eliminating the need of tedious work-up, and allowing an efficient subsequent one-pot anomeric substitution (Tai et al., 2003). Borontrifluoride etherate mediated glycosylation produced the thioglycoside **5** in excellent yield (90%) (Li, Huang, Hua, & Huang, 2009). Removal of the acetyl protecting groups was accomplished by conventional treatment of **5** with NaOCH₃. Finally, the methacryloyl function was introduced using



Scheme 1. Synthesis of methyl 6-*O*-methacryloyl- α -D-glucoside **2**.

the enzymic procedure described for the transformation of **1** to **2** (Albertin et al., 2004).

2.2. Synthesis of glycopolymers

For the polymerization of the monomers **2** and **7** in organic media, homogeneous solution polymerization was used (Schemes 3 and 4 and Table 1). It has been examined in the presence of AIBN as free-radical initiator in DMF at 70 °C, followed by precipitation in cold methanol (which was miscible with the monomers, the solvent, and by-products, such as oligomers). The attempt to homo-polymerize both monomers **2** and **7** under these conditions afforded only low molecular mass oligomer fragments, which was not possible to separate from the reaction mixture by precipitation. The co-polymerization with styrene (10 mol eq.) produced the solid polymers poly(methyl-6-*O*-methacryloyl- α -D-glucoside)-co-polystyrene **8** and poly(4-bromopheny-6-*O*-methacryloyl-D-glucoside)-co-polystyrene **11** in 50% and 38% yield with respect to the initial monomer mixture, and sugar content of 0.09 mol% in both polymers. They were soluble only in polar aprotic organic solvents, such as DMF and DMSO, and demonstrated very good swelling and water absorbing properties. In all co-polymerization procedures, random and uniform monomers distribution in the resulting polymer chains was ensured by thorough homogenization of the reaction mixtures by vigorous stirring.

Poly(methyl-6-*O*-methacryloyl- α -D-glucoside) **9** and poly(4-bromopheny-6-*O*-methacryloyl-D-glucoside) **12** were obtained by precipitation polymerization in aqueous media (Schemes 3 and 4 and Table 1). The monomers **2** and **7** were dissolved in oxygen-free H₂O under an argon atmosphere with sodium persulfate Na₂S₂O₈ (1%) as radical initiator, and heated at 70 °C for 24 h. The polymers were separated from the resulting heterogeneous reaction mixture by filtration, washed with cold methanol, and dried under vacuum. Polymers **9** and **12** were obtained in good yields (74% and 68%, respectively) and were characterized as amorphous solids.

For the co-polymerization of **2** and **7** with styrene in aqueous media, dispersion polymerization (Jung, Huh, Cheon, & Park, 2009) was performed to yield the polymers poly(methyl-6-*O*-methacryloyl- α -D-glucoside)-co-polystyrene **10** and poly(4-bromopheny-6-*O*-methacryloyl-D-glucoside)-co-polystyrene **13**. For this process two solutions were prepared: a water solution, containing the hydrophilic sugar monomer and the radical initiator sodium persulfate Na₂S₂O₈ (1%); and a toluene solution of styrene. An oil-in-water emulsion was formed by combining these two solutions and dispersing them by vigorous stirring. Then the emulsion was heated at 70 °C for 24 h while stirring vigorously. After cooling, the resulting heterogeneous mixture was treated as described above, to yield the polymers **10** (84%) and **13** (43%) as white powders.

The polymers **9** and **10** were insoluble in any solvent (probably due to the elevated molecular weight combined with the amphiphilic structure), which made their characterization difficult; while the polymers **12** and **13** were soluble in polar organic solvents, such as DMF and DMSO.

Using the monomers **2** and **7**, a series of polymers have been synthesized by free radical homo- and co-polymerization (Schemes 3 and 4 and Table 1). The polymerization conditions, reaction time, and the initial monomer ratios have been optimized as previously described (Barros, Petrova, & Ramos, 2004; Barros & Petrova, 2009; Barros, Petrova, & Ramos, 2007; Barros, Petrova, & Singh, 2010a,b). Homogeneous solution polymerization in organic media (DMF) and precipitation and dispersion polymerizations in aqueous media were studied. Polymers were obtained, with diverse glucose content (estimated by ¹H NMR), with different chain lengths, reported by the mass average molecular weight, *M*_w,

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